#47-1

PATENT
Attorney Docket No. 175912

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Boyd

Application No. 09/427,873

Filed: October 27, 1999

Group Art Unit: 1648

Examiner: J. Parkin

For: METHODS OF USING CYANOVIRINS TO INHIBIT VIRAL INFECTION

DECLARATION UNDER 37 C.F.R. § 1.132 OF MICHAEL BOYD, M.D., Ph.D.

1. I, Michael R. Boyd, am inventor of the subject matter disclosed and claimed in the above-identified patent application.

2. My education and experience are as set forth in the attached curriculum vitae.

3. Determining the appropriate dose and timing of administration of an antiviral agent to a host in order to reduce viral load is routine clinical practice in the field of antiviral therapy. With respect to cyanovirins, a clinician need only to perform a standard dose response study, which entails administering a range of doses of cyanovirin to a host and measuring viral load, to determine an appropriate dosing regimen to maintain cyanovirin levels such that a biological effect (e.g., a therapeutic effect) in the host is realized. A range of appropriate doses of cyanovirin is provided in the instant application. Means of determining viral load, in particular HIV viral load, are commercially available and routinely used in the laboratory. For example, the Amplicor HIV-1 Monitor test, better known as the PCR test, has been approved by

the Food and Drug Administration (FDA) as being appropriate for monitoring the efficacy of anti-HIV drugs. Viral load tests for viruses other than HIV also are available and require only routine laboratory techniques to perform. Therefore, the ordinarily skilled clinician has the requisite knowledge and ability to determine an appropriate dosage regimen to maintain sufficient cyanovirin concentrations to realize a biological effect (e.g., a therapeutic effect as evidenced by a reduction in viral load) in a host using only routine laboratory techniques.

4. I hereby declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 6/3/01

Michael R. Boyd, M.D., Ph.D.

#7-2

PATENT
Attorney Docket No. 175912

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Boyd

Application No. 09/427,873

Filed: October 27, 1999

Group Art Unit: 1648

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For: METHODS OF USING CYANOVIRINS TO INHIBIT VIRAL INFECTION

DECLARATION UNDER 37 C.F.R. § 1.132 OF MICHAEL BOYD, M.D., Ph.D.

1. I, Michael R. Boyd, am inventor of the subject matter disclosed and claimed in the above-identified patent application.

2. The data set forth below were generated under my direction.

3. One hundred nanograms of Ebola surface glycoprotein gp1-Z (strain Zaire 76), secretory Ebola surface glycoprotein sgp-Z (strain Zaire 76), HIV-1 glycoprotein gp41, HIV-1 glycoprotein gp120, and standard control peptides were incubated in 96-well Nunc-Immuno plates for two hours. The plates were washed with Tween/D-PBS and blocked with 1% BSA overnight. Following an additional wash, the plates were exposed to cyanovirin (100 ng/well) for 60 minutes. The plates were washed and incubated with anti-CV-N rabbit polyclonal antibody for 60 minutes. The plates were then washed and incubated with goat-anti-rabbit alkaline phosphatase- conjugated antibody for 60 minutes. After an additional wash step, the plates were incubated in a p-nitrophenyl phosphate color development solution until yellow substrate was observed. The reaction was stopped by adding 0.5 M EDTA,

and the absorbance was read at 405 nm using a SpectraMax 250 plate reader (Molecular Devices, Sunnyvale, CA).

4. Upon visualization of the ELISA reaction, binding of CV-N to all of the test proteins was detected, as illustrated by the attached graph. Absorbance was highest in those wells containing CV-N and Ebola gp1-Z glycoprotein and those wells containing CV-N and HIV-1 gp120 glycoprotein, indicating binding of CV-N to those surface glycoproteins. CV-N binding to HIV-1 gp41 and Ebola sgp-Z was also detected.

5. An affinity chromatographic system was constructed wherein rabbit anti-CV-N antibodies were coupled to Protein-A-sepharose in microcolumns (BioRad, Hercules, CA) according to the manufacturer's instructions. The columns were washed with TBS-T20 (Tris-buffered saline comprising 0.5% (v/v) Tween 20), and CV-N (0.4 μM, 2x50 μl) was added at five-minute intervals to the columns, with a corresponding volume of TBS added to a control column that was not exposed to CV-N. Following incubation with CV-N for 60 minutes at room temperature, the columns were washed with TBS-T20. Radiolabelled HIV-gp120 oligosaccharide samples or radiolabelled HSV-gC oligosaccharide samples (HSV is *Herpes simplex* virus) (100 ml) were added to the columns at five-minute intervals. After the final sample fraction was loaded, the samples were absorbed for 30 minutes at room temperature, after which the columns were washed with TBS-T20 until the radioactivity in the eluate reached background levels. Fraction volumes of 0.5 ml were collected and analyzed using a beta-counter. Materials bound to the columns were eluted from the

sepharose using 0.1 M glycin-HCl (pH 2.5), and elution fractions were analyzed for radioactivity using a beta-counter.

6. Using the chromatographic system described above, it was determined that radiolabelled HIV gp120 and radiolabelled HSV-gC oligosaccharides were captured by the column. In other words, the radiolabelled carbohydrates from HIV and HSV were bound by CV-N.

7. The results of the above studies indicate that CV-N binds carbohydrate components of glycoproteins of viruses other than HIV, and can bind carbohydrates of glycoproteins from which the proteinaceous component has been removed. The fact that CV-N binds glycans in the absence of any protein component indicates that CV-N will likely bind pathogens other than those specifically discussed herein.

7. I hereby declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 8/2/01

Michael R. Boyd, M.D., Ph.D.

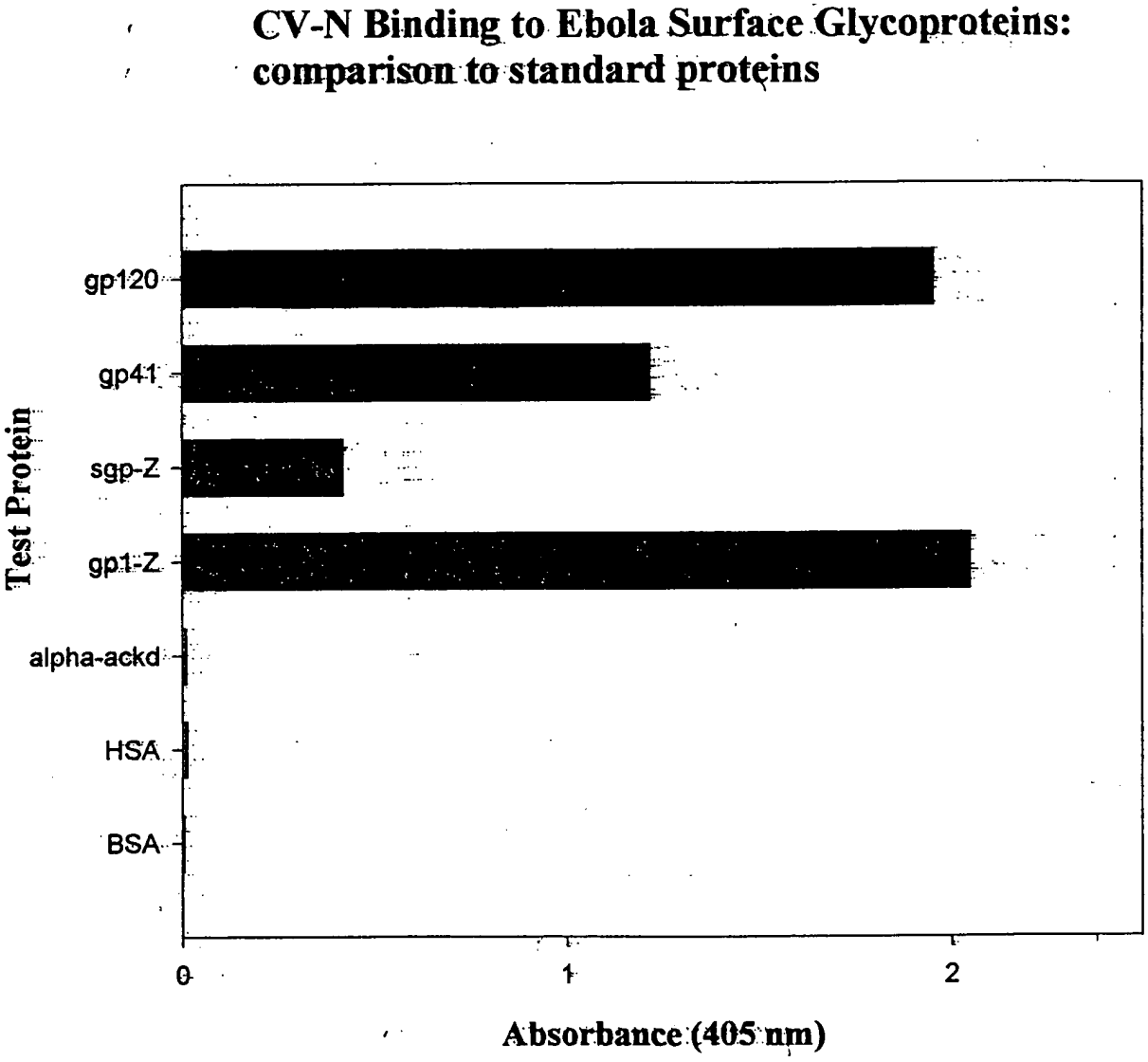

Figure 1 Legend: **BSA**: bovine serum albumin, **HSA**: human serum albumin, **alpha-ackd**: α-acid glycoprotein, **gp1-Z**: Ebola surface glycoprotein (strain Zaire 76), **sgp1-Z**: secretory Ebola surface glycoprotein (strain Zaire 76), **gp41**: HIV-1 glycoprotein gp41, **gp120**: HIV-1 glycoprotein gp120

Curriculum Vitae

July, 2001

NAME: Michael R. Boyd, M.D., Ph.D.

DATE & PLACE OF BIRTH: July 5, 1947, Cookeville, Tennessee

CITIZENSHIP: United States

MARITAL STATUS: Married, no children

EDUCATION:

May 1965	Graduated from high school
May 1969	B.S., Honors, Chemistry, University of Kentucky
May 1975	Ph.D., Pharmacology and Organic Chemistry, Vanderbilt University
May 1975	M.D., Vanderbilt University, School of Medicine

MEDICAL LICENSURE:

Current medical licensure in states of Tennessee (License Reg. No. MD0000009357) and Maryland (License Reg. No. D0024880); U.S. Controlled Substance Registration Certificate AB9301235

OTHER LICENSURE:

Licensed Commercial Pilot; FAA Certificated Flight Instructor

POSITIONS HELD:

1975-1977	Staff Fellow, Pharmacology/Toxicology Research Associate Program, National Institute of General Medical Sciences, and Laboratory of Chemical Pharmacology, National Heart, Lung and Blood Institute, Bethesda, Maryland
1977-1978	Senior Investigator, Clinical Pharmacology Branch, Clinical Oncology Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland
1978-1981	Head, Molecular Toxicology Section, Clinical Pharmacology Branch, Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland
1981-1984	Chief, Laboratory of Experimental Therapeutics and Metabolism, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland
1984-1990	Director, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland
1990-2001	Chief, Laboratory of Drug Discovery Research and Development, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, and Division of Basic Sciences, National Cancer Institute, Bethesda, Maryland
2001-date	Acting Director, Molecular Targets Drug Discovery Program, NCI Center for Cancer Research, National Cancer Institute, Bethesda, Maryland

COMMITTEE/ACADEMIC AND OTHER PROFESSIONAL APPOINTMENTS (Selected Listing):

Member, Scientific Advisory Panel, Chemical Industry Institute of Toxicology, 1980-1983

Member, Promotion/Tenure Review Committee, Division of Cancer Treatment, National Cancer Institute, 1983-1985

Chairman, Operating Committee, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, 1984-1987

Chairman, Biological Evaluation Committee, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, 1988-1990

Chairman, Decision Network Committee, Division of Cancer Treatment, National Cancer Institute, 1984-1987 (Member, 1981-1990)

Chairman, Screening Data Review Committee, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, 1990

Member, Commissioned Officers Promotion Review Board, United States Public Health Service, 1991

Preceptor, Pharmacology/Toxicology Research Associate (PRAT) Program, National Institute of General Medical Sciences, 1982-present

Chairman, Natural Products Research Committee, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, 1988-1996

Consultant and Grant Reviewer for the Arizona Disease Control Research Commission, State of Arizona, Phoenix, Arizona, 1990-present

Principal Collaborative Investigator, Indo-U.S. Agreement, U.S. National Institute of Mental Health, NIH, National Institute of Mental Health and Neurosciences, Bangalore, India, and National Brain Research Centre, New Delhi, India, 1992-Present

Member, Trans-NIH Microbicides Working Group, Office of AIDS Research, Office of the Director, National Institutes of Health, 2001-Present

EDITORIAL DUTIES (Selected Listing):

Member, Commentaries Editorial Advisory Board, **Biochemical Pharmacology**, Elsevier Press, 1996-present

Member, Editorial Board, **Biochemical Pharmacology**, Elsevier Press, 1982-1996

Associate Editor, **Journal of the National Cancer Institute**, U.S. Department of Health and Human Services, 1984-1991

Member, Editorial Board, **Fundamental and Applied Toxicology**, Society of Toxicology, 1981-1983

Member, Editorial Board, **Toxicology and Applied Pharmacology**, Academic Press, 1981-1983

Member, Editorial Board, **Experimental Lung Research**, Elsevier Press, 1980-1983

Member, Editorial Board, **Toxicology**, Elsevier Press, 1980-1983

MILITARY SERVICE:

Commissioned Officer, U.S. Public Health Service, 1974-2001; Permanent Corps, Research Officer Group; Permanent Rank, Captain, (O-6); PHS Ser.#42348; Retired, March 1, 2001.

PROFESSIONAL SOCIETIES:

Society of Toxicology
American Chemical Society
American Society of Pharmacognosy
American Association for Cancer Research
American Association for the Advancement of Science
American Society for Pharmacology and Experimental Therapeutics
American Society for Clinical Investigation

HONORS AND AWARDS:

Oswald (President's) Award for Undergraduate Research, University of Kentucky, 1969

Borden Research Prize in Medical Nutrition, Vanderbilt University, 1971

Vanderbilt Vivian Allen M.D.-Ph.D. Fellowship Award, Vanderbilt University, 1971-1975

The Achievement Award of the Society of Toxicology, 1979

The Commendation Medal, U.S. Public Health Service, 1979

Pfizer Award in Clinical Pharmacology, 1987

Pfizer Award in Pharmacology, 1988

The Meritorious Service Medal, U.S. Public Health Service, 1989

The Harold Lupiloff Award for Excellence in Clinical Oncology, 22nd Annual Detroit Cancer Symposium on Anticancer Drug Discovery and Development, 1990

Technology Transfer Award, U.S. National Cancer Institute, 1993

Technology Transfer Award, U.S. National Cancer Institute, 1994

RESEARCH INTERESTS:

Chemistry and bioactivity of natural products; anticancer, antiviral and antiparasitic drug discovery and drug development; *in vitro* and *in vivo* anticancer and AIDS-antiviral model development; high-throughput screening technologies; metabolism, pharmacology, molecular toxicology and experimental therapeutics of anticancer and anti-HIV agents; extrahepatic mechanisms of xenobiotic metabolism, toxicity and carcinogenesis; pathogenesis and therapy of lung cancer; prostanoid biosynthesis and metabolism in neoplasia

LECTURES PRESENTED AT MAJOR SYMPOSIA (Selected Listing):

Invited lecture, Symposium on "Target Organ Toxicity: Lung" September 16-17, 1975, Cincinnati, Ohio

Invited lecture, Gordon Conference on Drug Metabolism July 10-15, 1977, Plymouth, New Hampshire

Invited lecture, Symposium on "Clinical Biochemical Pharmacology of 5-Fluorouracil and Anticancer Pyrimidines" July 22-23, 1978, Marseille, France

Invited lecture, International Symposium of the Princess Takamatsu Cancer Research Fund on "Naturally Occurring Carcinogens-Mutagens and Modulators of Carcinogenesis", January 23-25, 1979, Tokyo, Japan

Invited lecture, Symposium on "The Scientific Basis of Toxicity Assessment", April 15-19, 1979, Gatlinburg, Tennessee

Invited lecture, Symposium on "Environmental Toxicology", January 19,1979, Burlington, Vermont

Invited lecture, Ciba Foundation Symposium on "The Toxicological Significance of Interaction of Environmental Chemicals with Drug-Metabolizing Enzymes", October 23-25, 1979, London, England

Invited lecture, The Ninth Annual Meeting of the New England Pharmacology Society, January 25-26, 1980, Storrs, Connecticut

Invited lecture, ACS Symposium on "The Pesticide Chemist and Modern Toxicology", June 26, 1980, Dowington, Pennsylvania

Invited lecture, Second International Symposium on "Biological Reactive Intermediates", July 14-17, 1980, Guildford, United Kingdom

Invited participant, Interagency Task Force on Environmental Cancer, Heart, and Lung Disease, Workshop on "Exposure, Metabolism and Mechanisms of Toxicity", January 27-30, 1981, Rockville, Maryland

Invited lecture, International Symposium on "Chemical Indices and Mechanisms of Organ-Directed Toxicity", March 4-7, 1981, Barcelona, Spain

Invited lecture and co-chairman, Symposium on "Nonrespiratory Metabolic Functions of the Lung", Annual Meeting of the Federation of American Societies for Experimental Biology, April 12-17, 1981, Atlanta, Georgia

Invited lecture, Symposium on "Biological Kinetics of Chemically Reactive Metabolites", November 1-6, 1981, Sarasota, Florida

Keynote address, Symposium on "Metabolite-Mediated Toxicity", 15th Annual Meeting of the Australasian Society of Clinical and Experimental Pharmacologists, December 14-16, 1981, Adelaide, South Australia

Invited lecture, Symposium on "Toxicity Testing; New Approaches and Applications in Human Risk Assessment", September 14-15, 1983, St. Louis, Missouri

Invited lecture, International Meeting on "Chemical Carcinogenesis II, Xenobiotics and Biotransformation", October 12-15, 1983, Sasari, Italy

Invited speaker, General Motors Conference on "Cancer Therapy, Where Do We Go From Here", September 14-15, 1984, Jackson Hole, Wyoming

Chairman and speaker, NCI Workshop on "Disease-oriented Antitumor Drug Discovery and Development", January 9-10, 1985, Bethesda, Maryland

Invited speaker, US-Japan Joint Seminar, February 25-26, 1985, Oahu, Hawaii

Invited lecture, 4th World Conference on Lung Cancer, August 25-30, 1985, Toronto, Canada

Invited lecture, International Union Against Cancer (UICC) - Study Group Meeting, September 9-11, 1985, Oslo, Norway

Invited lecture and co-chairman, FASEB Summer Conference on "Lung Pharmacology", July 28-August 1, 1986, Saxton's River, Vermont

Invited speaker, First Beijing International Symposium on "Cancer Treatment and New Trends of Cancer Chemotherapy", September 7-9, 1986, Beijing, China

Invited lecture, Fifth NCI/EORTC Symposium on "New Drugs in Cancer Therapy", October 22-24, 1986, Amsterdam, The Netherlands

Chairman and speaker, NCI/NIAID Workshop on "Issues for Implementation of a National Anti-HIV Preclinical Drug Evaluation Program; Critical Parameters for an *In Vitro*, Human Host-cell Based, Primary Screen", April 8-9, 1987, Rockville, Maryland

Pfizer Lecture in Clinical Pharmacology, University of Mississippi Medical Center, May 18-19, 1987, Jackson, Mississippi

Chairman and speaker, NCI Workshop, "Issues Concerning Selection, Characterization and Quality Control of Human Tumor Cell-Lines for the National Cancer Institute's New Drug Screening Program", May 27-28, 1987, Bethesda, Maryland

Invited lecture, EORTC Pharmacokinetics and Metabolism (PAM) Group Symposium, June 18, 1987, Lyon, France

Invited lecture, Workshop of the EORTC New Drug Development and Coordinating Committee (NDDCC), June 19, 1987, Lyon, France

Invited lecture, 57th ANZAAS Congress, James Cook University of North Queensland, August 28, 1987, Townsville, Australia

Pfizer Lecture in Pharmacology, Texas Tech University School of Medicine, May, 1988, Lubbock, Texas

Invited lecture, Society of Toxicology Symposium on "AIDS Drug Development and Toxicology", March 2, 1989, Atlanta, Georgia

Invited lecture, Sixth NCI EORTC Symposium, on "New Drugs in Cancer Therapy", March 7-10, 1989, Amsterdam, The Netherlands

Invited lecture, US-Japan Cooperative Cancer Research Program, Seminar on "Marine Natural Products and Cancer", March 23-24, 1989, Oahu, Hawaii

Invited lecture, Japanese Foundation for Cancer Research Symposium on "Cancer Chemotherapy", April 19-21, 1989, Tokyo, Japan

Invited lecture, American Association for Cancer Research Symposium on "Prediction of Tumor Response", May 25, 1989, San Francisco, California

Keynote address, 20th Symposium on "Drug Metabolism and Drug Action and Toxicity", October 12-13, 1989, Sapporo, Japan

Invited lecture, Phase I-II Study Group of the Medical Association of International Medicine, November 23-24, 1989, Frankfurt, Germany

Invited lecture, Twenty-Second Annual Cancer Symposium on "Anticancer Drug Discovery and Development", April 26-28, 1990, Detroit, Michigan

Invited lecture, Gordon Conference on "Marine Natural Products", February 17-21, 1992, Ventura, California

Invited participant, National Heart, Lung and Blood Institute Working Group on "Pulmonary Complications Associated with Breast Cancer Therapy", September 20, 1993, Rockville, Maryland

Invited participant, International Conference on "Oxidative Stress in HIV Disease", November 8-10, 1993, NIH, Bethesda, Maryland

Invited lecture, Symposium on "Intellectual Property Rights for Naturally Derived Bioactive Compounds and the Conservation of Biodiversity", October 21-24, 1994, San Jose, Costa Rica

Plenary lecture, Symposium on "Natural Products Research", DECHEMA, Chemische Technik and Biotechnologie, February 22-24, 1995, Kaufbeuren, Germany

Dedication Address, ASU Cancer Research Institute Facility, Phase I, Arizona State University, Tempe, Arizona, April 23, 1996.

Invited lecture, "Ernest Guenther Award Symposium", 215th National Meeting, American Chemical Society, March 29-April 2, 1998, Dallas, Texas

Invited participant, Symposium on "Anti-HIV Microbicides", NIAID/WHO, May 19-20, 1998, Atlanta, Georgia

Plenary lecture, 9th International Symposium on "Marine Natural Products", July 5-10, 1998, Townsville, Australia

Invited lecture, Symposium on "Advances in Transfusion Safety", March 18-20, 1999, San Francisco, California

Invited speaker, Alliance for Microbicide Development, May 10-11, 1999, Washington, D.C.

Plenary lecture, Symposium on "New Prospects in Anticancer Agents", American Chemical Society National Meeting, March 26-31, 2000, San Francisco, California.

Dedication Address, ASU Cancer Research Institute, Arizona State University, March 6, 2001, Tempe, Arizona.

Invited lecture, NIAID Collaborative Antiviral Testing Group (CATG) Annual Meeting, National Institute of Allergy and Infectious Diseases, NIH, May 9-10, 2001, Bethesda, Maryland.

Invited lecture, UICC International Cancer Congress, June 30-July 5, 2002, Oslo, Norway.

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PATENTS AND PATENTS PENDING

Boyd, M.R., Cardellina, J.H., Snader, K.M., Gustafson, K.R., Patterson, G.M.L., McMahon, J., Weislow, O.S., Shoemaker, R.H., Paull, K.D.: **Antiviral Compositions Containing Sulfoquinovosyl Glycerol Derivatives and Analogs Thereof and Methods for Using.** U.S. Patent Application No. 07/393,780, August 15, 1989; PCT International Patent Application No. PCT/US90/04270, August 3, 1990; International Publication No. WO 91/02521; European Patent Application No. 90911868.5; Canadian Patent Application No. 2,064,772; ***Japanese Patent No. 2022435, issued May 24,1995; Australian Patent No. 635057, issued July 5, 1993.***

Vistica, D.T., Scudiero, D.A., Monks, A.P., Skehan, P.J., Boyd, M.R.: **CO_2-Independent Growth Medium for Maintenance and Propagation of Cells.** U.S. Patent Application 07/467,939, January 22, 1990; U.S. Patent Application No. 07/742,077, August 7, 1991; PCT International Patent Application No. PCT/US91/00451, January 22, 1991; International Publication No. WO 91/10726; U.S. Patent Application No. 08/164,687, December 9, 1993; Canadian Patent Application No. 2,074,363. ***Australian Patent No. 653927, issued February 15, 1995; Japanese Patent No. 2074371, issued July 25,1996; European Patent No. 0512066, issued November 13, 1996.***

Boyd, M.R., Cox, P.A., Cragg, G.M., Blumberg, P.M., Sharkey, N.A., Ishitoya, J., McMahon, J.B., Beutler, J.A., Weislow, O.S., Cardellina, J.H., Gustafson, K.R.: **Antiviral Composition.** U.S. Patent Application No. 07/530,562, May 30, 1990; U.S. Patent Application No. 08/424,558, April 17, 1995; PCT International Patent Application No. PCT/US91/03619, May 24, 1991. ***Japanese Patent No. 2020302, issued February 19, 1996; Australian Patent No. 639343, issued November 12, 1993; Canadian Patent No. 2,083,945, issued February 7, 1995; European Patent No. 0531413, issued August 28, 1998; U.S. Patent No. 5,599,839, issued February 4, 1997.***

Boyd, M.R., Cardellina, J.H., Manfredi, K.P., Gulakowski, R.J., McMahon, J.B., Blunt, J.W., Pannell, L.K., Cragg, G.M.: **Michellamine Antiviral Agents, Composition and Treatment Methods.** U.S. Patent Application No. 07/684,197, April 12, 1991. PCT International Patent Application No. PCT/US92/02805; European Patent Application No. 92922789.0. ***Japanese Patent No. 1957368, issued August 10, 1995; Australian Patent No. 657549, issued July 4, 1995; Canadian Patent No. 2,100,066, issued August 13, 1996.***

Boyd, M.R., Cardellina, J.H. II, Gustafson, K.R., McMahon, J.B., Fuller, R.W., Cragg, G.M., Kashman, Y.: **Calanolide Antiviral Compounds; Compositions and Use,** U.S. Patent Application No. 07/861,249, March 31, 1992; PCT International Patent Application No. PCT/US93/02810, March 24, 1993; Australian Patent Application No. 39355/93; Canadian Patent Application No. 2,133,080. ***European Patent No. 0633887, issued May 19, 1999; Japanese Patent No. 3103114, August 20, 2000.***

Boyd, M.R., Cardellina, J.H. II, Fuller, R.W., Snader, K.M., Clardy, J.: **Novel Antitumor Compound, Compositions and Method of Use.** U.S. Patent Application No. 07/835,637, April 23, 1992; PCT International Patent Application No. PCT/US93/01283, April 6, 1993; Canadian Patent Application No. 2,129,956; European Patent Application No. 93906963.9; Japanese Patent Application No. 514303/1993. ***Australian Patent No. 657614, issued August 15, 1995; U.S. Patent No. 5,283,383, issued February 1, 1994.***

Boyd, M.R., Cardellina, J.H. II, Gustafson, K.R., Decosterd, L., Parsons, I.C., Pannell, L.K., McMahon, J.B., Cragg, G.M.: **Antiviral Naphthoquinone Compounds, Compositions and Uses Thereof.** U.S. Patent Application No. 08/011,183, January 29, 1993; PCT International Patent Application No. PCT/US94/01119, January 31, 1994; Canadian Patent Application No. 2,155,020; International Publication No. WO 94/17055, August 4, 1994. ***European Patent No. 0681578, issued July 5, 1997; Australian Patent No. 680872, issued December 4, 1997; Japanese Patent No. 2922648, issued April 30, 1999; U.S. Patent No. 5,672,607, issued September 30, 1997.***

Boyd, M.R., Cardellina, J.H., Manfredi, K.P., Blunt, J.W., Pannell, L.K., McMahon, J.B., Gulakowski, R.J., Cragg, G.M., Bringmann, G., Thomas, D., Jato, J.: **Michellamine Antiviral Agents, Composition and Treatment Methods.** U.S. Patent Application No. 08/049,824 [Continuation-In-Part of 07/684,197], April 19, 1993; PCT International Patent Application No. PCT US93/03682, April 19, 1993; International Publication No. WO 94/24108, October 27, 1994; Canadian Patent Application No. 2,160,869. ***U.S. Patent No. 5,455,251, issued October 3, 1995.***

Boyd, M.R., Cardellina, J.H. II, Gustafson, K.R., McMahon, J.B., Fuller, R.W., Cragg, G.M., Kashman, Y., Soejarto, D.: **Calanolides and Related Antiviral Compounds, Compositions and Uses Thereof.** U.S. Patent Application No. 08/065,618 [Continuation-In-Part of 07/861,249], May 21, 1993; PCT International Patent Application No. PCT/US94/05658, May 18, 1994; International Publication No. WO 94/28000, December 8, 1994. ***Japanese Patent No. 2852706, issued November 20, 1998; Australian Patent No. 685468, issued January 22, 1998; European Patent No. 0699202, issued March 3, 1999; Canadian Patent No. 2,163,348, issued February 1, 2000; U.S. Patent No. 5,591,770, issued January 7, 1997.***

Boyd, M.R., François, G., Bringmann, G., Hallock, Y., Manfredi, K., Cardellina, J.H. II: **Antimalarial Korupensamines and Pharmaceutical Compositions and Medical Uses Thereof.** U.S. Patent Application No. 08/195,260, February 14, 1994; PCT International Patent Application No. PCT/US95/01853, February 13, 1995; Japanese Patent Application No. 521405/1995; European Patent Application No. 95909553.0; International Publication No. WO 95/21826, August 26, 1998. ***Canadian Patent No. 2,183,247, issued August 17, 1999; Australian Patent No. 690640, issued September 10, 1998; U.S. Patent No. 5,409,938, issued April 25, 1995.***

François, G., Bringmann, G., Phillipson, J.D., Boyd, M.R., Timperman, G., Schneider, C., Ake Assi, L.: **Antimalarial Naphthylisoquinoline Alkaloids and Pharmaceutical Compositions and Medical Use Thereof**. U.S. Patent Application No. 08/195,547, February 14, 1994; PCT International Patent Application No. PCT/US95/01717, February 13, 1995; European Patent Application No. 95910230.2; Japanese Patent Application No. 521360/1995; Canadian Patent Application No. 2,183,155; International Publication No. WO 95/21616, August 17, 1995. ***Australian Patent No. 690967, issued November 5, 1998; U.S. Patent No. 5,639,761, issued June 17, 1997.***

Bringmann, G., Götz, R., Boyd, M.R.: **Monomeric Naphthylisoquinoline Alkaloids and Synthesis Methods Thereof**. U.S. Patent Application No. 08/279,291, July 22, 1994. PCT International Patent Application No. PCT/US95/09132, July 19, 1995; European Patent Application No. 95928091.8; Japanese Patent Application No. 505844/1996; Canadian Patent Application No. 2,195,647; International Publication No. WO 96/03382, February 8, 1996; ***Australian Patent No. 709428, issued August 26, 1999. U.S. Patent No. 5,552,550, issued September 3, 1996.***

Bringmann, G., Harmsen, S., Boyd, M.R.: **Dimeric Naphthylisoquinoline Alkaoids and Synthesis Methods Thereof**. U.S. Patent Application No. 08/279,339, July 22, 1994. ***U.S. Patent No. 5,571,919, issued November 5, 1996.***

Bringmann, G.R., Boyd, M.R., Gotz, R., Kelly, T.R.: **Dimeric Arylisoquinoline Alkaloids and Synthesis Methods Thereof**. U.S. Patent Application No. 08/363,684 [Continuation-In-Part of 08/279,291 and 08/279,339], December 23, 1994; PCT International Application No. PCT/US95/09070, July 19, 1995; European Patent Application No. 95927269.1; Japanese Patent Application No. 505832/1996; Canadian Patent Application No. 2,195,646; International Publication No. WO 96/03381, February 8, 1996. ***Australian Patent No. 699121, issued March 11, 1999; U.S. Patent No. 5,578,729, issued November 26, 1996.***

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CURRENT COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENTS (CRADA's):

CRADA Title: **Conjugation of Cyanovirin-N and Derivatives Thereof with Poly(Ethylene Glycol) for Use Against the Human Immunodeficiency Virus (HIV)**. Collaborating organizations: U.S. National Cancer Institute (NCI) and Shearwater Polymers, Inc., Huntsville, AL. NCI Principal Investigator, Michael R. Boyd, M.D., Ph.D.; Collaborator Co-principal Investigators, Michael J. Roberts, Ph.D., and J. Milton Harris, Ph.D..

CRADA Title: **Development of a Novel HIV/Cell Fusion Screening Assay and Application to Screening the NCI Natural Products Repository**. Collaborating organizations: U.S. National Cancer Institute (NCI) and Panacos Pharmaceuticals, Inc., Gaithersburg, MD. NCI Co-principal Investigators, James B. McMahon, Ph.D., and Michael R. Boyd, M.D., Ph.D.; Collaborator Co-principal investigators, Carl Wild, Ph.D., and Graham Allaway, Ph.D..